DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

SINGLE ISSUE FOCUS MEETING

SECTION 401 OF THE FDA MODERNIZATION ACT:

DISSEMINATION OF INFORMATION ON

UNAPPROVED/NEW USES FOR MARKETED

DRUGS, BIOLOGICS, AND DEVICES

Department of Health and
Human Services
Wilber Cohen Building
330 Independence Avenue, S.W.
Snow Room
Washington, D. C.

Wednesday, July 8, 1998
1:30 p.m.

P R O C E E D I N G S

(1:40 p.m.)

MR. GAYLORD: We're going to go ahead and get started for this afternoon.

First of all, let me say good afternoon to each of you. It's a pleasure to see that so many people Were able to come out this afternoon.

I'm Charles Gaylord, the Acting Associate Commissioner for Consumer Affairs. On behalf of the Food and Drug Administration, I'd like to welcome each of you to today's meeting to discuss the proposed rule, Dissemination of Information on Unapproved or New Uses for Marketed Drugs, Biologics, and Devices, more simply known as off-label use promotion.

This afternoon, I will co-moderate today's program along with Sharon Smith Holston, the Deputy Commissioner for External Affairs.

And joining us is Bill Schultz, the Deputy Commissioner for policy, who will give an overview of the proposed rule.

In addition, we have other agency experts that are part of the working group charged with drafting this rule and helping to implement it. They are seated at the table to my right. I will introduce. We have Peggy Dotzel, who is the working group chairperson, along with Philip Chao, both from the Office of Policy. In addition, we have Seth Ray from the Office of General Counsel, along with Larry Braslow from Office of Planning and Evaluation. And representing the relevant centers, Drugs, Biologics, and Devices, respectively, we have Bob Temple and Laurie Burke, Tonia Stifano, and Jay Crowley.

One of the main priorities that the Office of Consumer Affairs has is to facilitate a dialogue between the public and FDA so that they have a part in the decision-making process within the Agency. Toward that end, this meeting has been convened to enable consumers and others to better understand the proposed rule and to have a chance to comment on it. After our National Consumer Forum which was held in March

of this year, consumer groups requested that such a meeting be held. Initially we planned to have a forum for consumers as well as patient advocates, but there is so much interest in this rule that we opened it up so that everyone such as health professionals and industry representatives could also attend. So we're glad that so many are here today to talk about this rule.

Since the FDA Modernization Act of 1997 became law, the Agency has worked diligently to provide guidance and regulations on implementing its provisions. Of course, Section 401 with off-label usage is one of the more controversial provisions of the Act itself. So, we'd like to hear your comments about it, as well as answer questions that you may have.

Before opening up the program itself, I'd like to bring out a few points:

First of all, on the tables on the outside

we have additional copies of the Federal Register notice, along with copies of the press release. We tried to give those out to you before you came in, but if anyone did not get copies, they're on the table outside.

Next, the meeting is divided into three parts and will last no longer than three hours. Given the air conditioning of the building, or lack thereof, that's a good length for today's meeting. We have allotted time so that those who preregistered and asked to give comments will have time to do that, as well as others in the audience who would like to present their comments. Toward that end, we ask that you keep the comments fairly brief, no more than five minutes, so that everyone who would like to give their comments will have the chance to do so. We've provided the microphone in the center aisle for your convenience, and all of the comments will be transcribed.

This entire meeting is being transcribed and will be part of the rule-making process.

We would also invite each person to send in your written comments to the docket so that it would also be part of the written record as well. Copies of the transcript will be available. We had a sign-in sheet for those who would like a copy to be sent to you. They will be available in the next few days, and it will also be available by writing and requesting them through the Dockets Management Branch at the address listed on the F.R. notice.

I would now like to go into the meeting itself. I have the pleasure of introducing to you, the Deputy Commissioner for External Affairs, Sharon Smith Holston.

So I will now turn the program over to her.

Sharon?

MS. HOLSTON: We're trying to get a few more chairs into this room so that those of you in

the back can have a modicum of comfort for the rest of the afternoon.

Good afternoon and thank you again very much for coming. As Charles pointed out, this is part of an ongoing dialogue that we'd like to have with consumers and other constituencies of the Agency to discuss what's going on in the Agency, particularly those things that are of significant interest to the outside community.

As I will discuss in just a minute, this dialogue that we've historically had for a long time, is about to become a lot more intense, in just the next couple of months.

This meeting, obviously, is to discuss 401 of the Act, and it was in response to numerous requests that we were receiving, particularly from the consumer community and from the patient advocacy community to have a better understanding of this particular provision of the Act which defines the conditions under which manufacturers can disseminate information about off-label indications for

unapproved--I'm sorry, off-label indications for approved drugs, biologics and medical devices. And as Charles also said, this is a provision that really has engendered quite a bit of controversy.

As some of you may well remember, FDA in the past was somewhat opposed to this particular provision, and it was our position that with the exception of independent educational events where health professionals were being presented with carefully balanced, scientifically rigorous, non-promotional kinds of information, the dissemination of information by manufacturers about uses that were not approved by the Agency was simply not authorized. And one main reason for that was our concern that if manufacturers were able to disseminate this kind of off-label information about their products without doing the studies that would be necessary to actually support those, that they wouldn't be inclined to do those. The doctors and patients would not have the benefit of that kind of clinical data in order to help them in informed prescribing. Patients,

in many cases, who would use these particular products, sometimes would be denied compensation by health insurers who only would pay for FDA-approved products and for FDA-approved indications.

Section 401, we believe, addresses these concerns by authorizing the dissemination of reliable and balanced information about the safety, effectiveness, and benefits of unapproved indications, provided that the manufacturer has committed to do the research necessary to support a submission to the Agency for a supplementary approval.

Bill is going to talk to you about this in more depth in just a minute. What I would like to mention, however, is that as I said earlier, in just a few weeks, as a matter of fact, you're going to be hearing a lot from us about another part of FDAMA, and that's Section 406(b).

As you know, FDA has a broad range of responsibilities under the Food, Drug, and Cosmetic Act, as well as other acts that we're responsible for

implementing. Knowing that we have this huge laundry list of responsibilities that are mandated by statute, and that in some cases, FDA has difficulty meeting all of its statutory obligations, Congress also put into FDAMA, a provision that we would, in fact, consult with our stakeholders.

The statute specifically identifies the stakeholders as scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups, and the regulated industry. We would consult with these stakeholders, and following these consultations, come up with a plan that would be published in the Federal Register and submitted to Congress by November 21st of this year. In that plan, we would, in fact, describe how we're going to meet our obligations under the laws that we're charged with implementing. We're not going to do the discussion of that plan today, but I did want to let you know that in the next couple of weeks, you will be probably receiving an invitation from the Agency to participate in one or

more different meetings which are part of this stakeholder consultation process.

Each one of our Centers is planning on having a separate meeting with stakeholders who have a particular interest in their area. The Center for Food Safety has already had one meeting. But the others will also be holding meetings, and we will also be having one large public meeting, all in an effort to get input from our stakeholders for the development of this plan which we will be submitting to Congress.

We want to make certain that all of you have an opportunity to participate in that process. When you see the invitation, there will be a notice coming out in the Federal Register that will have the dates and the locations of all of the meetings, and we will hope you will take advantage of that opportunity, because we really do want to hear from you in that process.

So, without further delay, I'm going to turn it over to Bill Schultz, who was instrumental in

helping to craft the FDAMA legislation. He will talk to you about Section 401.

MR. SCHULTZ: Thank you Charles and Sharon, for organizing this, and for the introductory remarks. As Sharon indicated, there has been a lot of interest as we can see by the number of people here and the number of people standing. There is a lot of interest in this regulation and in this provision.

That's not a surprise because there was a lot of interest in it when it was enacted as a part of the FDA Modernization Act. It was very controversial. It was very difficult to work out and reach a compromise, too.

It is a provision that is very important to both its supporters and people who have doubts about it.

But our job as the Agency now is not to support it or oppose it, but to implement it. Fortunately, Congress was very detailed when it wrote this provision, which makes our job somewhat easier. But our job is to understand what the intent was,

which was to provide circumstances where journal articles and certain other scientific information, particularly in textbooks, about unapproved uses of drugs could be disseminated to physicians and health professionals.

Unfortunately, Congress also gave us a very short deadline to issues those regulations. The law was passed, and signed, I guess, on November 21, 1997.

We usually think that if we can do a rule-making in two years, that's very quick. And the most of the bill gave us about that time frame to do regulations, but this provision has to be implemented within one year.

We have with this bill, taken these deadlines very, very seriously, and we intend to do everything we can to meet them.

Consistent with that, we published the proposed rule at the end of the first week of June of this year. Unfortunately, we were only able to provide 45 days for comment instead of the usual 75- or 90-day comment period. When you add to that the time for the Agency to write a proposed and final rule and

to clear those through the Agency, the Department and the Office of Management and Budget, that kind of comment period just wasn't realistic.

So it's a shorter comment period than usual. It's good--I hope it helps somewhat that we've scheduled this meeting, as this is another opportunity to get comments. But the comment period expires the 23rd of July, and while we're already getting requests to extend it, I just don't think that's going to be possible to extend it and still meet this kind of deadline.

So, we want to urge people to get their comments in on time, to give us very full comments. I am sure that aspects of this rule will be changed between the proposal and the final, and the comments typically make a very big difference in what the final outcome of the regulation is.

What I'd like to do is spend a few minutes and just talk about the proposal, which is also talking about the statute. As I said, in most of these cases, the statute has spoken in quite a bit of

detail. As everybody here knows, the purpose of

this provision is to change the rules. The rule previously prohibited a drug manufacturer from distributing a journal article or textbook about a use of a product that hadn't been approved by FDA.

This statutory provision allows distribution of that kind of information. And it allows it, if the information is scientifically sound and it's balanced.

So if there are two articles going in opposite directions, they both have to be distributed, and if it contains, a disclaimer, it's clear to the recipient that the use hasn't been approved by FDA, even if it also contains the official labeling, or the approved labeling for the product.

In addition, FDA can require an additional objective statement be distributed as well. In other words, the FDA can say in order to balance this information, that there is some additional information the physician would need to know.

The company that wishes to distribute this kind of information is to submit it to FDA 60 days in advance of actually disseminating it, and it is to

provide FDA with the information that's going to be disseminated, with other information it has about the use of the product that's in the article, and, in particular, information about any adverse effects.

In addition to that, the company must have done one of three things: It must have already submitted a supplement for the use. So that means it's done the full studies of the use and actually submitted them for approval to the FDA, but it's waiting on FDA's decision.

Or it can say, well, we've--we're actually currently doing the work; we're almost done, and we'll get the supplement to FDA within six months.

Or, third, it can say, well, we haven't done the studies, but we'll do them, the studies that are designed to show this use. And in connection with that, the company would provide FDA with the protocol and schedule for doing the studies, which are to be submitted with a supplement within three years.

Now, that last requirement does not have

to be met if the company can qualify for one of two exemptions: That is, if it can show either that to do the study would be unethical, or economically prohibitive.

We, typically in this kind of rule-making, don't get the comments until the last day of the comment period. But we've gotten a few already. And they range. As is typical in some cases, a commenter will do what we think is over-reading a requirement that's in our regulation. And a commenter does that because they're trying to be very careful to make sure of what we mean.

As you go to the final, the final gives the opportunity to clarify exactly what the Agency did mean. So, for example, we've gotten one comment from a number of different places that we're being too prescriptive in what kind of article is going to qualify, and that the requirements that we have set will exclude most articles that are in--even those that are in New England Journal of Medicine and very

reputable journals.

That is not the intent of the proposal. I mean, we'll go through this and make decisions as we go through each submission, but in terms of the proposal, the expectation would be that most of the full blown articles in that kind of journal would, in fact, qualify.

Another area we've gotten comments on was completely expected, and that is the definition of economically prohibitive. We found that to be one of the most difficult issues we had to address.

We put forward a proposal, we put forward some other options, but we are very much seeking input on that and other ideas as to exactly what the right test is.

I'm going to stop now, because we want to spend most of this meeting listening to you. Because we're in the middle of a rule-making, we won't engage in sort of a back and forth discussion or debate.

We want to hear your comments. The panel may have questions. People from the Agency may have

questions of the commenters, but basically what we want to do is listen to what you have to say. There are two people who signed up to make comments, and so I think we'll start with them, and then others who want to can do so.

The two who signed up are Russell Bantham from Pharma, and Brad Thompson.

So, Russ, do you want to start?

MR. BANTHAM: Thank you, Bill. My name is Russell Bantham. I'm here on behalf of the Pharmaceutical and Research Manufacturers of America. First of all, I want to commend the FDA for providing this forum, and giving us and others the opportunity to provide input.

We will be submitting detailed comments to the Docket by the July 23rd date, as you have given. I have more formal comments which I'd like to submit for the record today, but with your permission, I will not read them or go through them in detail, if that's all right.

We will also post these comments on the

Pharma website, so they are available--will be available to everyone by tomorrow.

I'd just like to make a couple of general comments. This section on dissemination is really about getting the latest and best medical and scientific information to health care professionals so that it can be provided to patients. That is how we look at this section.

We believe it was intended by Congress to balance two very important objectives: First of all, to facilitate the sharing of this important treatment information with health care providers to enable better patient care.

And, two, to ensure that research leading to new labeled uses continues to be undertaken. Our feeling is that the proposal that has been put forward, goes beyond the carefully defined statutory scheme and imposes significant requirements and constraints on those two objectives.

We think that Congress established detailed but rather straightforward statutory schemes

for manufacturers to notify the Agency of their intent to disseminate information on new treatment uses, and for FDA to make a determination about whether the proposed dissemination was objectionable.

We think FDA's proposal goes well beyond the notification and review procedure that Congress envisioned.

We think Congress' intent was to allow the dissemination of information that manufacturers could previously only distribute in response to an unsolicited request for the same information from a health care provider.

FDA appears to be treating dissemination of this kind of information as ordinary promotion. The introductory comments referred to this as promotion.

We feel that there's a difference between the dissemination of scientific and medical information through the use of peer-reviewed, qualified reprints and reference texts.

A further comment on what we believe is

the failure of the Agency to recognize the difference between promotion and dissemination: We believe that dissemination is essentially being able to do proactively, what companies are now permitted to do reactively; that is, to provide this scientific and medical information that qualifies, proactively to health care providers, whereas we can now only provide it in the context of a reaction; that is, when a formal request is made.

I think it is very important to reexamine the whole thrust of the proposed rule in terms of this distinction.

Secondly, we think the rule, the proposed rule, virtually bans the use of reference texts which we think Congress clearly intended to permit the dissemination of, and we also think that it is overly restrictive on the dissemination of journal articles.

We think the proposal, as Bill referenced, does provide too difficult a hurdle for the exemption for supplements which are economically prohibitive.

Third, we think the proposal requires

unduly restrictive mandatory statements.

Lastly, we think the proposal defines new uses so broadly that information on approved uses could potentially fall within the regulations.

With that, I think I will stop, and have my comments submitted for the record.

MR. SCHULTZ: Thank you, that's great. Let me ask if anybody has any questions?

MR. TEMPLE: Could you say a little bit more about what the aspects of the rule that restricts journal articles? There's one paragraph, basically, that describes what a journal article has to have in it.

MR. BANTHAM: Well, the law, we believe, requires that the journal article be about a clinical investigation that would be considered scientifically sound by experts.

We think the language as in the proposed rule calls for a reasonably comprehensive presentation of the study design, conduct, data, analysis, and conclusion.

We think that many articles don't have that information; that the peer review process sort of examines whether or not that's available, and one could read all of those requirements as essentially imposing a level of detail and a level of requirements that most journal articles would have trouble meeting.

MR. TEMPLE: So it's the phrase, "reasonably comprehensive," that has you worried?

MR. BANTHAM: That's correct.

MR. TEMPLE: And you presumably would like some clarification?

MR. BANTHAM: That's correct.

MR. TEMPLE: You're not saying it shouldn't tell you who is in the study?

MR. BANTHAM: Oh, absolutely not. If it's there in the reprint, that's great.

MR. TEMPLE: I need to be sure. You wouldn't say the reprint is adequate if it doesn't say what the patient population is going to be; it's how comprehensive it has to be?

MR. BANTHAM: That's correct.

MS. STIFANO: Could you also comment on why you feel that it virtually would ban the use of reference texts?

MR. BANTHAM: The way the criteria are set forth, I don't believe most texts would fit with the criteria, or comply with those criteria. Texts are not usually about clinical studies.

Most of the texts are--

MS. STIFANO: The preamble does give a bit of an explanation about how they can be used, you know, under normal circumstances, they wouldn't normally fit, but it does give an explanation as to how they could, in fact, be utilized; would you not agree?

MR. BANTHAM: In the preamble of the text itself, it is not at all clear that most textbooks, most standard textbooks would qualify. It's a question that we have in reading the text, in reading the proposal, as you put it forward.

MR. SCHULTZ: Thank you.

MR. BANTHAM: Thank you.

MR. SCHULTZ: Bradley Thompson was the other. If you could identify yourself and who you represent?

MR. THOMPSON: I'm Brad Thompson. I'm representing a group called the Indiana Medical Device Manufacturers Council, which is a trade association of about 60 companies.

May I ask a preliminary question of the Chairman, I guess? There's a little confusion about what kind of a meeting this is. Some people have been calling it a Part 16 meeting. I don't think that's right. Could you clarify what kind of meeting this is? Anyone?

MS. HOLSTON: This started out as what we were calling a single-issue focus meeting, primarily directed at consumers. We have expanded it to include all of our interested constituencies, but it's a meeting for us to hear from you --we will have a transcript of the meeting, and we will include the comments in the Docket, but it is not a formal Part 16 meeting.

MR. THOMPSON: Thank you.

Probably to most people's disappointment, I come here to say absolutely nothing about the off-label reg itself, but to talk about this meeting and how the meeting is being organized.

I'm sorry to take us on that tangent, but I came about 500 miles to say this.

I want to start off by congratulating the FDA on the efforts over the last several years to involve the public in a very direct way in the development of regulatory positions. The Indiana group petitioned several years ago for good guidance practices, and there are several people sitting at that table, the table in front, who were very involved in coming up with what I thought was a very excellent set of good guidance practices.

We've raised issues about the advisory committee process and about public participation. There is a theme, though, to what we are saying.

The theme is that out in Indiana, we need a little bit more notice than four days in order to

be able to attend and participate in a meaningful way in very important meetings such as this one.

We heard about the meeting as a result of the Federal Register Notice published last Tuesday. With the federal holiday in between, that means essentially four business days before this meeting was to convene.

As a trade association, I'm afraid, although I'm the General Counsel of it, they don't give me carte blanche to say whatever I want to say.

We're very member-driven, so in order for me to participate in a meeting like this, I have to first caucus with my people, get them to build a consensus on what ought to be said, and then communicate it. And four days isn't possibly enough time to do anything like that. I think the fact that you see only two people having pre-registered is some evidence of what I'm saying.

Now, there may be people who are willing to stand up and say things off the cuff, but for an organization such as a trade association to

participate, we need a little bit more notice. I understand that the FDA is under time pressure in order to respond to the Congressional deadline, and I know that it's a year deadline. I know that there's a 45-day comment period.

But when a 45-day comment period is offered up, the way we process that is by starting on that 45th day and working backwards to make sure we complete our process by that time. At this point, in the middle of the meeting, we have nothing to say. I'm very much afraid that this is a real opportunity lost. Your time is very precious. We've got all the right people in the room from the FDA. But we don't have any meaningful comment to offer you. I would urge you that it's not because we don't have thoughts on the matter; we do have thoughts. We just aren't able to express on them notice offered.

I'll offer one parenthetical, and that is that it isn't enough that we're entitled to make

written comment. These meetings, when they are organized in this way, create opportunities for dialogue which when people outside the Beltway aren't able to participate, that's an opportunity lost and not to be regained.

There's a lot of loss surrounding the fact that written comments after the fact do not make up for an adequate notice before the fact.

Again, I want to thank you for the meeting. The meeting is a great idea. The notice left a lot to be desired.

MR. SCHULTZ: I think that was a fair point. We had not intended to have a public meeting on this rule-making. We generally haven't done it. There was a real demand for it, and we were just put in a situation where we either had to do something which you see as inadequate, and I can understand why you're saying that, or not do it at all.

If there are other people, though, who have comments, we are certainly very interested in them.

In the time frame, we're just doing the best we can do. But I understand what you're saying, and I think they're fair points.

Does anybody else have anything that they'd like to say? If you do, why don't you just come up to the microphone.

Maybe people can line up two at a time or so. If everybody would try to keep their comments to five minutes or less, we'd appreciate.

What I'd ask you to do is identify yourself and your organization before you start.

MS. COHEN: Well, I'll identify myself as

a consumer member of an advisory panel. I have no affiliation with any--can you hear? You look like you're having problems.

MR SCHULTZ: Your name?

MS. COHEN: That would help, wouldn't it? My name is Susan Cohen. I am the wife and the mother of scientists. I've been surrounded by science for 42 years.

I am also from a consumer protection background, and I've seen what self-policing doesn't do. I am very concerned that this could erode and undermine the whole process for drug approval.

There is an article in the New York Times I'll refer you to. It's May 30th, 1998, and it refers to the risks to patients in drug trials and the monitoring and the review boards.

I think you should read it because this all goes back to how it all starts to begin with. So the Journal of the American Medical Association says, there are a hundred thousand Americans who have adverse reactions to drugs, and it is the fourth or

sixth cause of death. This was done in hospitals. It did not include what was done at home. So we don't know exactly what people are dying of, and off-label use, I've heard everybody uses it. I have probably been the recipient of it.

There are inadequate funds for research in the safety of drugs after the FDA approval. I think MedWatch has a budget, if I'm correct, of $148,000.

Physicians are not required by law to report adverse reactions. I'm afraid physicians don't read the journals very much. That concerns me. And with HMOs and doctors seeing how many patients in an hour, are they going to read, are they going to know what they're doing? Are they going to understand what they're doing?

Drug manufacturers are going to be the main source of information? And who is going to monitor them?

And how much money is involved in this?

Can industry really police and monitor themselves when huge sums of money are involved?

Reference articles-- it concern me about the literature. Scientists read literature. Their life depends upon it. They publish.

Physicians don't publish, they don't have to read the literature. It isn't required.

I have asked on occasion--I am a consumer who can ask questions. But how many consumers can ask adequate questions? What do they know to ask?

The industry is trying to teach consumers to ask questions. But if a physician really doesn't know what the adverse reactions are of off-labeled drugs, do you want to take it?

That should be your decision to make. And I have always been taught that drugs were supposed to be safe and effective and the tests are supposed to be done in a diversity of population.

Is that going to happen?

I have real concerns about what's going to happen, and I am very concerned that consumers are at the bottom of the scale again, when politics and money enter into it. I want to protect consumers, and I

want consumers to know when it's prescribed to them, there have not been adequate tests, there have not been clinical trials.

And when they take it, they should make the decision, do I want to take this drug, not knowing what adverse reactions there might be? Thank you very much.

DR. SCHULTZ: Does anyone have questions or comments? Dr. Temple?

DR. TEMPLE: I do. Are there particular aspects of the -- we're faced with a law that says reprints will be handed out under some circumstances, so we don't get to decide that anymore.

Are there particular things in our regulation proposal that you think should be altered or should be enhanced, that would resolve any of these concerns?

MS. COHEN: You know, I am concerned about self-policing. I think you ought to go talk to the Federal Trade Commission about expecting people to submit information six months later or three months

later.

It concerns me. I have done, although I'm not an attorney, I have done a lot of cease and desist agreements, and I think you ought to know what you've got before you enter into anything.

I am very, very concerned about that. I mean, we can talk about historical effects of thalidomide and all the other things that have been on the market, but I think something has to be on the market quite awhile before you know what the adverse reactions are.

And will off-label use be done immediately? When a new drug comes on the market, will you immediately allow off-label use promotion? Or are you going to wait a period of time before you see if there are side effects.

I'm really, really concerned about this because somehow, in the back of my mind, I think FDA is going to erode it's authority, you're going to turn it over to other aspects of society who have other interests. Yes, there's a good side and a bad

side to this dissemination.

I come from -- my husband was at NIH. I know the research he did. I know the publications that he did. Nothing was published unless it had validity to it. And I am concerned that we're going to be protected, and I worry mightily about the stock market and what that affects in terms of what you're going to do. I can't help it, that's how I look at it.

So I think off-label use, I know, I've had a few discussions with friends actually about it, and I know that it can be efficacious and I know that it does help, but how far do you go if you haven't done all the clinical trials, and you haven't done the diverse population and you really don't know if it's safe and effective.

You know it for something specific, but are you going to know it for the off-labeling, and you're going to depend upon the information that comes later?

Are you sure you're going to get the information?

Is it going to be correct?

And what can you do quickly if there is a problem?

Those are my concerns. I don't know if that answers your question or not. I didn't mean to ramble, but did I do it?

DR. TEMPLE: Well, not really. I understand your general concerns about the change in the law. And as Ms. Holston said in the first place, it is controversial--

MS. COHEN: Yes.

DR. TEMPLE: I guess the one thing I hear from you is that you think we ought to make sure the schedule for information that comes in is attended to. That is certainly part of it.

MS. COHEN: Absolutely. Absolutely. It must be complied with. And if you give extensions and extensions and extensions, it isn't as though it's something minor, it's something very important and I think they have to comply with the information in a timely fashion.

MR. DIXON: I'm Carl Dixon, the President of the Kidney Cancer Association. Kidney cancer is a rare disease by definition.

There are about 100,000 cases in the United States. The most widely prescribed medication for kidney cancer is off-label for kidney cancer.

We are very supportive of these rules. We think they will go a long way towards enabling medical practitioners to find out what treatments there are for kidney cancer and other diseases.

We are somewhat concerned by the narrowness or what we perceive to be the narrowness of the journals that would be permissible.

And I understand from Dr. Schultz's earlier comment that that issue is being looked at, so I will not go into that in more detail.

Generally, we want to commend the Agency for doing we think a very craftsman-like job on drafting these regulations.

Thank you. Questions?

(No response.)

DR. SCHULTZ: Anybody have a question?

(No response.)

DR. SCHULTZ: Thank you very much.

MR. BLOOM: Hi. I'm Jeff Bloom from Project Inform in the patients' coalition that was characterized as a bogus coalition that was politically astute by a member of the audience here. And I'm not surprised for industry to squeal about being accountable for anything and opposing parts of these regulations.

I think we have two major concerns.

One is that off-label doesn't become a back door for disseminating information on populations that aren't included in original clinical trials.

What comes to mind right now is the Viagra situation. We have a large amount of people that were excluded from the clinical trials that weren't contraindicated for the use of the medication.

In the labeling, it doesn't say anywhere in any place that we haven't tested in these

populations; it should say "Use at your own risk."

And I'm not saying it's a problem in these populations, but it simply was a part of the exclusion of the criteria for the trials. And I would think it would be helpful if off-label information was labeled as indicated as saying that this was done in a population that was not a part of a clinical trial, and also the source of the information is of great concern.

And I know part of this isn't supposed to be about the plan, and I think a lot of us probably felt part of this is, you know, how is this going to be implemented.

But on a very, very basic level, I think that we're terrified that you have ten people in DDMAC that are going to be reviewing off-label pharmaco-economics, direct-to-consumer television advertising, and how is it remotely possible that you're going to be capable of policing this in any way, shape or form in any sort of comprehensive fashion, given the resources you have now?

Because to those of us in the patient community, we see this as an impossible task. I think you guys do the best that you can, but ten people to supervise a $125 billion industry with the amount of information that comes out seems impossible, and I'd like to hear your comments about it.

MR. SCHULTZ: Does anybody have any questions?

DR. TEMPLE: Just one thing. It's not true that DDMAC will be responsible for looking at the scientific quality of all these articles.

The things come to them because that's appropriate, but they will then be making use of all the rest of us to look at the articles. We only have 60 days but --

MR. BLOOM: Right. But you have ten people that basically have to, at the end of this food chain, review all these materials. Those ten people in that office are the ones that say yea or nay to whether these are going to go forward.

DR. TEMPLE: No, that's not correct.

MR. BLOOM: Okay. Well, if you could elaborate on how this is actually going to work, that would be very helpful, because you know, DTCA is a huge market obviously that they're going to get pounded on in this review. I assume that's going through DDMAC.

Television advertising is a whole new field which obviously the first round of the TV ads had to be changed and pulled and adapted.

But it seems like really, you know, mostly the only things that you can actually have any effect on are when problems are brought up to you. But your ability to be pro-active about this is virtually non-existent because of the resources issue.

DR. TEMPLE: Well in this case there is a specific submission that is required under this new law before a particular article or a reprint can be transmitted that will go to DDMAC. But the ordinary review committee will then be looking at it.

There may be some initial screening by

DDMAC but the scientific soundness will be assessed and be applied by the people who usually assess scientific soundness.

Again, I'm not trying to minimize the level of effort. It depends on how many come in, but it is not just those ten who try to do it all. That is not true.

MR. BLOOM: But after the 60 days, it's approved by default, though, if you don't comment? It gets tacit approval, right?

DR. TEMPLE: Yes. But we will always comment.

(Laughter.)

DR. MURPHY: Mr. Chairman, my name is Dr. Martin Murphy. In this capacity, I'm representing, as the Executive Editor of the peer-reviewed cancer journal entitled The Oncologist, which is a journal directed to the practitioner who is daily in charge of the care of cancer patients.

I rise personally, and in that capacity as editor, and also professionally, to salute not only

this forum, but your tack that you're taking in soliciting dialogue.

Since it is incumbent upon the peer review of outstanding journals to authenticate to the best of human ability that which is going to be in the best interests of humankind in this regard of medicine.

It is really important also that if there are some guidelines, that at the end of all of this you can give to the editors of peer reviewed journals that might, in some fashion, facilitate the kinds of questions that you're going to have to be answering, or the kinds of analyses to which you are going to put the petitions placed before you by the pharmaceutical companies, we would be only too pleased to review those.

It may, hopefully through this dialogue and subsequent dialogues, facilitate being able to enhance, if you will, that which is already a well-honed process of peer review.

That is a petition or an offer that

certainly I can extend on behalf of our journal, and I believe I speak collegially for many other journals, not only in cancer.

I have one question and it deals with the criteria that are apt to be used for the identification of those journals which would pass your peer review and therefore be authenticated, if you will, as those journals that you would accept as having met a standard of excellence that you would then be comfortable with.

If there is any commentary on that, or if you could direct us to information, I would also be very appreciative.

Thank you.

MR. SCHULTZ: I think your idea is very interesting.

Does anybody else have questions or comments?

(No response.)

MR. SCHULTZ: Thank you very much.

MR. SANDERS: Good afternoon. My name is Scott Sanders. I'm with the American Foundation for AIDS Research and the Patients' Coalition.

We have numerous concerns about the regulations, but I think it was Dr. Temple who said most of those decisions were already made by Congress in what we think was a very short-sighted process.

But one specific concern or question I have is the transparency of the process.

Under the Regs, industry is required to submit clinical trial designs, letters or statements requesting why they shouldn't have to do the research, why it would be prohibitive in terms of economics.

How much of that will be available to the public to look at?

I think it has already been mentioned that we are afraid that the Agency has far too few resources to do an adequate job of policing this process, and we feel that as the patient community, it is also going to be incumbent upon us to be involved in that process.

In the past, we have had a very hard time

accessing some of this information from the Agency. So I am wondering, I didn't see any reference in here as to what information will be public and what will not be public, and I am wondering if someone could address that.

MR. SCHULTZ: Well, I mean, I think that is exactly the kind of thing we need to consider as we go to the final rule, and we will consider it as your oral comment, and if you want to submit something in writing, we will consider it that way as well.

MR. SANDERS: So you don't see this necessarily as proprietary, or can you lay out what you see as proprietary or not?

DR. SCHULTZ: I just don't think it is something we should be answering here. I don't believe we've addressed it in the proposal, but I think it is something that is very appropriate for you to raise and for us to address.

DR. TEMPLE: Could I just say one quick thing?

Is the particular thing that you thought was of most interest the use of the economic exemption?

MR. SANDERS: Well it is certainly one that concerns us. I mean, it is sort of a new barometer. I mean for a normal approval, you've got to prove it's safe and effective. There's no economic test. And so now we're raising the hurdle to say you have to prove it's safe and effective unless it's going to cost too much money.

And for people that are going to be taking those drugs, that doesn't make any sense, but as you said, it's what's written in the law, so you had to address it in the regs, and you know, we're still looking at how you addressed it, and whether or not we think that's the appropriate way to do it. But if companies are going to be filing that information, we feel that as the community, we have a right to look at that and say, this is not true, the patient population is larger or, you know, they're going to be charging a lot more,

whatever.

We just think that if that process is completely locked away from us, it leaves us sort of out of the process and we have, you know, the whole phase four stuff now where we can't access that information.

And again, we're going to have trials that are going forward and they have to be done in three months, and there's going to be progress reports. We'd like to see those progress reports.

DR. TEMPLE: Okay. So the things you identify particularly are, one is the basis for an economic exemption?

MR. SANDERS: Any exemption; right.

DR. TEMPLE: Yes, and--

MR. SANDERS: It's about standard of care and--

DR. TEMPLE: Well, the other is that exemption.

And the third thing you identify is the timing of the submission.

MR. SANDERS: Right. The progress reports

and also what studies they say they're going to complete or that they're going to do over the next three years, what those studies look like, and then subsequently how the progress is going, and if there's a problem, if they ask for a two-year extension.

MR. SCHULTZ: I would ask you to look at this. I mean, there are obviously serious issues of proprietary data and any suggestions you have for us about where we ought to draw these lines, what we ought to make public and what we should not, and when, would be helpful.

MS. NELSON: My name is Jill Nelson and I'm a nurse with an MBA, going back to law school now, and I had the honor of working with the FDA/CDRH for the summer, but I do not represent them, this is a personal opinion.

One of my concerns that I think all of us share is that drugs meet the cost requirements and that we're giving the care that we need to give.

What I'm curious about is, going back to

unapproved and new uses, is to do a better job of post-marketing surveillance.

And I'm wondering if there's any thought been given to changing some of the prescribing habits of physicians to try to work with the AMA, to have physicians write what a drug is being prescribed for so that could be entered into a database with pharmacies, that that would provide data to industry, so that maybe we could avoid some of these expensive studies and do some retrospective research.

Thank you.

DR. TEMPLE: I don't know of any immediate thought on that, but you know there are surveys that at least for the more common drugs do allow you to know what drugs are being prescribed for. Laurie Burke has actually made some use of that, and you can discover, to a degree, what drugs are used for. But having it on the prescription would be a whole new order of magnitude of information. There is no question about that.

But I don't know of any in terms of planning to pursue that.

MR. SCHULTZ: Now, you know this provision sunsets in eight years, and at the end of that period of time, a study will be done on how it played out. That's probably a lot longer time period than what you're looking for, but you know, there's a required look at it at that point in time.

Is there anyone-- Yes, good.

MS. FOSTER: Good afternoon. I am Michelle Foster from Biogen. I'm representing the Mass Biotech Council.

We actually have a question.

We recognize that clinical information must be submitted within 36 months of dissemination as a supplement for approval, and we know that FDA's criteria for acceptable articles are criteria that are appropriate for meeting the standards for supplements to submit for a labeling change.

However, prior to doing the necessary

studies for FDA approval, the Act allows for dissemination of articles that are scientifically sound.

These could potentially be derived from IND or non-IND studies that may not necessarily meet FDA's criteria and your proposed guideline, but they meet strict publication peer review criteria.

So we're wondering why FDA wouldn't allow dissemination of this information with appropriate fair balance provided, and that fair balance would include the known safety and efficacy and perhaps state what isn't known yet so that a risk assessment could be presented.

MR. SCHULTZ: I think that is the kind of question we will have to answer in the final rule, but we will look at the words of the statute to make sure it is scientifically sound, and we are obligated to make that judgment as to whether the article is scientifically sound or not.

But that is the kind of issue I am sure we will respond to and consider.

suggest it has to be part of an IND. I think we can answer that.

But I mean this really is the kind of issue we want to work out as we go through to the final regulation.

MS. FOSTER: Well, I have--

DR. TEMPLE: Excuse me. Is it possible you are referring to the preamble? When you read the proposed rule, I can't figure out what you're worried about.

MS. FOSTER: Um-hmmm. Okay.

DR. TEMPLE: We can't respond to it unless we know what you are worried about.

MS. FOSTER: Well, along with the rest of us, I didn't have a lot of chance to do as much study as I would like. So we are really asking for a clarification.

But I have in my notes the clinical studies prospectively plan according to a protocol; there's--

DR. TEMPLE: That's in the preamble.

MS. FOSTER: Right.

DR. TEMPLE: And that analysis is well documented case series, appropriately defined diagnosed patient population, accounting for all patients enrolled, utilizing clinical end points or surrogate end points, well-described treatment regimen, using an appropriate control group, and so on. So you're saying that was in the Act?

MR. SCHULTZ: No. It is in the preamble. But if you think it is too restrictive, then you need to tell us--and you're telling us to some extent now--but, you know, that is part of what happens between a proposed rule and a final rule.

We will in the final rule look at it, we

will make changes when appropriate, and we will explain why we are making changes, or why we think it is consistent with the statute.

But I think we all need to just continue--we need to do this, and everybody needs to continually go back to that statute and say, you know, what kind of test is going to be true to the statute that Congress enacted.

MS. FOSTER: Thank you.

MR. SCHULTZ: Thank you.

DR. TEMPLE: I think you really need to be more specific. I mean, some of the things you read about regarding defining the population, that is not hard to do that. But proving you had the protocol and followed it, I can see where you would be worried about that. So it is very important to say which parts you feel are troublesome.

MS. FOSTER: Okay. Thank you.

MS. HOLLAND: Hi. I am Elaine Holland with the American Academy of Pediatrics. I just wanted to offer a brief comment.

The Academy of Pediatrics was very much involved throughout the legislative process-- throughout this implementation process in the Food and Drug Administration Modernization and Accountability Act.

Section 401 of the Modernization Act is of great concern to the Academy, particularly in light of the fact that 80 percent of the drugs used in the pediatric population are used off-label. So the impact of this particular provision is something of great concern to the Academy and to children specifically.

So we will be offering extensive and detailed comments on this issue. But I just wanted to mention that we were pleased with the Pediatric Study's exclusivity piece within FDAMA, and we are offering our comments in some ways to suggest the crosswalk of the provision of Section 111 and 401 in the FDA so that there will be a compatibility and an acknowledgment of the importance of the two provisions as it relates to children's health and the

therapeutic advances.

Thank you.

MR. SCHULTZ: Any questions?

(No response.)

MR. SCHULTZ: Thank you, very much.

MS. CALMS: My name is Jennifer Calms. I am a reporter with BNA's Health Care Policy Report.

When you say "dissemination," what mediums are you talking about? Are you including the Internet on that?

(Pause.)

(Laughter.)

MR. SCHULTZ: There is a shudder in the room.

(Laughter.)

MR. SCHULTZ: I think that what was imagined was drug companies distributing journal articles to physicians and other health care professionals.

We will have to look at questions like how the Internet fits into that. That is a good question

for a comment.

MS. CALMS: I have an additional question for Robert Temple. You mentioned you do have other resources than the ten folks at DDMAC. Can you give an inventory? Like is it 12 people in one center, and 20 in another? What other resources do you have?

MS. STIFANO: Four people in Center for Biologics that will be the recipients of the information--

MS. CALMS: Four people from where? I'm sorry, I didn't get that.

MS. STIFANO: The Center for Biologics. We will be the recipients and again triage the information and get it out to the appropriate medical officers within the three divisions.

So our goal is to process and triage those applications that are complete, and get it off to the medical officers as soon as humanly possible.

MS. CALMS: How many medical officers do you have?

MS. STIFANO: Per office? It varies per office.

MS. CALMS: Across FDA?

DR. TEMPLE: Hundreds.

MS. STIFANO: Hundreds.

DR. TEMPLE: CEDA has a couple hundred, plus appropriate numbers in biostatisticians. It is the same crowd of people who would do INDs, NDAs, and all the rest of it. Divisions may well have a special cadre of people to work on this, and that would be up to them, but it is the entire review staff that is available.

MS. CALMS: So you're essentially saying you are going to access hundreds of folks who are going to be involved in this.

MS. STIFANO: Yes. It is really no different than any submission. The same personnel that would be reviewing any other application will be involved.

MS. CALMS: Thank you.

MR. SCHULTZ: Let me just mention one

other thing on the Internet. We have a separate process that will likely lead to some kind of guidance as to what sort of promotion and other dissemination of information is permitted on the Internet.

We had a public meeting on that, a two-day meeting on it about a year-and-a-half ago, and something will likely come out of that that may address this, as well.

MS. CALMS: Are you officially dovetailing together, or working together?

MR. SCHULTZ: No--well, officially--

MS. CALMS: Well, not "officially."

MR. SCHULTZ: It's not officially, but...

MS. CALMS: Thank you.

MR. WALDMANN: Daniel Waldmann with McKenna & Kuneo.

I was just looking for a little clarification, or any response about the fact that medical devices that are being marketed under a 510(k) and have a new off-label indication that would require a PMA will not be eligible.

I don't remember that being discussed while the bill was being worked on, and I think it might reflect an overly technical reading of the statute, and I was wondering, one, to say I think that in the final rule, to the extent the agency thinks that that is what was intended, there needs to be more discussion of what you think the justification is on that.

Otherwise, I think that issue needs to be revisited.

MR. SCHULTZ: Can you say the issue again?

MR. WALDMANN: With relation to a 510(k) device out on the market--

MR. SCHULTZ: Why don't you tell people here what a 510(k) is?

MR. WALDMANN: A device that is being marketed because it is substantially equivalent to something that was on the market before 1976, in general--

MR. SCHULTZ: Okay.

MR. WALDMANN: --and a new indication that

was not--the new indication that was off-label would not have been part of that pre-1976 indication and it would therefore need a premarket approval application.

MR. SCHULTZ: And the question is whether you could distribute a journal article about that--

MR. WALDMANN: Correct.

MR. SCHULTZ: --use that has not been approved?

MR. WALDMANN: Correct.

MR. SCHULTZ: Okay.

MR. WALDMANN: And the agency's belief that that type of application or that device would not be included within the definition of a "supplement" so that you wouldn't be able to file a supplement and you would then not be eligible under the statute.

DR. TEMPLE: Okay. That is something we will certainly take a look at.

MR. WALDMANN: Thank you.

MS. HARVEY: Michelle Harvey with Glaxo-

Welcome.

I have a question about a 60-day review period. The regulation talks about "for purposes of this part, a submission shall be considered to be complete if FDA determines that it's sufficiently complete to permit a substantive review."

I wondered if you could comment a little bit about what you will take into consideration so industry will have a better idea of when that 60-day period actually does begin.

MR. SCHULTZ: I think what would be better would be for you to suggest to us--it doesn't have to be here--what you think ought to qualify, or what criteria you think ought to be included in the regulation.

MS. HARVEY: I guess I would--

MR. SCHULTZ: I mean, if you feel that the proposal does not give adequate guidance, then you need to say that. But I think you also, if you like, could suggest what you think would be helpful.

MS. HARVEY: Because I think most people would hope that when they submitted the application that it was complete when they submitted it--

MR. SCHULTZ: Right.

MS. HARVEY: --and that therefore the clock would actually start on receipt of the application.

MR. SCHULTZ: That is what we would expect.

MS. HARVEY: Okay. But I guess some of us were concerned--

DR. TEMPLE: As long as it is sufficiently complete.

MR. SCHULTZ: Right.

DR. TEMPLE: There is a list of things that have to be in it.

MS. HARVEY: Correct.

DR. TEMPLE: And that is what needs to be there. But, as we've said, if you think it needs more clarification, you need to point out the parts that need clarification.

MS. HARVEY: Well, I don't know--I think

it was included in the "sufficiently complete," and what does that really mean? Was that meant to give some leeway there so that if time is running out the FDA would determine that it wasn't sufficiently complete, when in fact all the pieces were actually there.

I think we need some definitive time point of when the time clock begins so we can plan, and we will include those comments in our submission.

MR. SCHULTZ: Okay. I mean, the intent of the statute is there is a time period, and the intent was that it actually runs.

MS. HARVEY: Thanks very much.

MR. SCHULTZ: Thank you.

MR. BRENNER: My name is Ted Brenner. I'm with Environment Corporation. We do scientific and regulatory consulting.

I just have a brief comment, or maybe it is a question, actually, about the supplemental NDA submission provisions of the proposed rule.

That is, it doesn't mention or seem to address the literature-based supplemental NDAs, which is I guess an idea that's been rumbling around the agency for the last couple of years.

I know it probably--I mean it wasn't, as far as I know, specifically mentioned in the Act itself, but it seems to kind of dovetail nicely with this whole dissemination and the type of information that will be required to be submitted for getting approval for that dissemination.

I just wondered if FDA had considered that at all, and whether that would be appropriate for inclusion in this type of ruling.

DR. TEMPLE: We just put out in final form our--I can't remember the precise title--but what we call the evidence document which describes the circumstances in which the literature-based submission will be persuasive.

So we didn't think this phrased that issue in any novel way; it is the usual issue, and that document tells what we think are the circumstances in

which that will move ahead.

MR. SCHULTZ: And in referring to a submission of a supplemental NDA on the current proposed rule, that could be a literature-based supplemental NDA if the conditions were such that it was allowed.

DR. TEMPLE: If you are familiar with that document, it basically says that literature often misses certain kinds of information in the protocol.

MR. BRENNER: Right.

DR. TEMPLE: And that it might be usual to ask for at least some additional information, much of which would be available for recent publications.

But it also says that there's a lot of data, and others might do it, but those are the principles and they just have to change that.

MR. BRENNER: Okay. Thanks.

MR. SCHULTZ: Let me just ask how many more people intend to speak?

(No response.)

(Laughter.)

MR. SCHULTZ: Does anybody else want to say anything?

(No response.)

MR. SCHULTZ: Okay, and we probably do not need to take a break.

Sharon, did you want-- Charles?

MR. GAYLORD: First of all I would like to thank each of you for attending this afternoon, and to thank you for providing the comments that will be taken into account as this Rule moves forward toward final implementation.

We regret the lack of seating and apologize for that. And with regard to the lead time, we are sorry there was such a short lead time. We feel that providing these opportunities are extremely important to incorporate the ideas and suggestions of our constituents, and we anguished about that as we planned this meeting.

We realized that there was going to be a short lead time, but we thought it was very important

to go ahead and have the meeting and to have it across the spectrum in terms of all of our constituents.

I would like to thank each of our panelists who were here from the Agency, and Dr. Robert Temple who has answered many of your questions and comments.

We appreciate all of our panelists for being here, and Bill Schultz who has worked long and hard on FDAMA.

In the upcoming months as we have additional meetings, we will inform you about them and invite you again to participate.

I want to close on the note of Conversations with America.

This Administration has focused very much on the fact that Government needs to listen to its citizens and, toward that end, the National Partnership for Reinventing Government has stressed that in order for Government to be effective it has to listen to those that are affected by its

procedures, its policies, and its decisions.

By your being here and providing your comments, you have given us an opportunity to listen and to take into account your comments on the provisions of an Act that, as we said at the outset, is controversial in some measures. But as a public health protection agency, the FDA puts a premium on its regulatory responsibility.

Despite the resource constraints and the ever-increasing workload, protection of the public health will continue to be our highest priority.

As we look ahead to the summer, we will have additional meetings. We will be holding district consumer forums in the field where regional issues will be discussed.

We will have a National Consumer Forum in September.

These are just two small examples of how FDA is reaching out to its stakeholders--consumers, health professionals, and industry representatives in an effort to better do its job.

Thank you for being here this afternoon, and please enjoy your evening.

(Applause.)

(Whereupon, at 2:50 p.m., Tuesday, July 9, 1998, the meeting was adjourned.)

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